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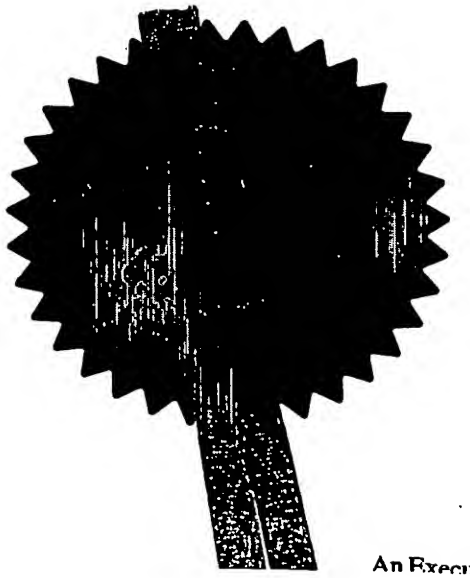

Signed Andrew Guy

Dated 2 April 2004

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P01/7700 0.00-0314697.4

Patents Form 1/77

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Request for grant of a patent

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1.	Your reference	4-33239P1/HO 81
2.	Patent application number *(The Patent Office will fill in this part)*	24 JUN 2003 0314697.4
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND
	Patent ADP number *(if you know it)*	
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND
4.	Title of invention	Organic Compounds
5.	Name of your agent *(If you have one)* "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH
	Patents ADP number *(if you know it)*	1800001

Novartis Pharmaceutic
UK Limited
Patents and Trademark
Wimblehurst Road
Horsham West Sussex
RH12 5AB

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application		Number of earlier application	Date of filing (day/month/year)
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes		

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Continuation sheets of this form	
Description	16
Claim(s)	2
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature: B.A. Yorke & Co.

Date: 24 June 2003

B.A. Yorke & Co.

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. S. Schnerr
020 8560 5847

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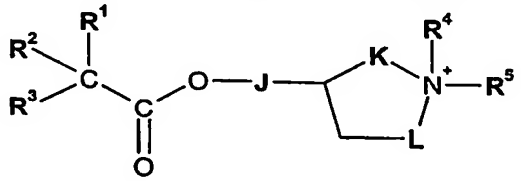
ORGANIC COMPOUNDS

This invention relates to organic compounds, their preparation and use as pharmaceuticals.

In one aspect the invention provides compounds of formula I



I

in salt or zwitterionic form wherein

R^1 and R^3 are each independently a C_3-C_{15}-carbocyclic group or a 5- to 12-membered heterocyclic group having at least one ring heteroatom selected from nitrogen, oxygen and sulphur;

R^2 is hydrogen, hydroxy, or C_1-C_4-alkyl optionally substituted by hydroxy;

J and K are both independently C_1-C_2-alkylene,

or one of J and K is a bond and the other is C_1-C_2-alkylene;

L is C_1-C_2-alkylene;

R^4 is C_1-C_4-alkyl;

R^5 is C_1-C_8-alkyl substituted by $-OR^6$, $-O-CO-R^6$ or $-CO-O-R^6$; and

R^6 is C_1-C_8-alkyl, a C_3-C_{15}-carbocyclic group or a 5- to 12-membered heterocyclic group having at least one ring heteroatom selected from nitrogen, oxygen and sulphur.

Terms used in the specification have the following meanings:

"Optionally substituted" means the group referred to can be substituted at one or more positions by any one or any combination of the radicals described.

"Halo" or "halogen" as used herein denotes an element belonging to group 17 (formerly group VII) of the Periodic Table of Elements, which may be, for example, fluorine, chlorine, bromine or iodine. Preferably halo or halogen is fluorine, chlorine or bromine.

"C_1-C_8-alkyl" as used herein denotes straight chain or branched C_1-C_8-alkyl, which may be, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, straight or branched pentyl, straight or branched hexyl, straight or branched heptyl, or straight or branched octyl. Preferably, C_1-C_8-alkyl is C_1-C_4-alkyl.

"C_1-C_2-alkylene" as used herein denotes alkylene that contains one or two carbon atoms, i.e. methylene or ethylene.

"C_1-C_8-alkoxy" as used herein denotes straight chain or branched C_1-C_8-alkoxy which may be, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, straight or branched pentoxy, straight or branched hexyloxy, straight or branched heptyloxy, or straight or branched octyloxy. Preferably, C_1-C_8-alkoxy is C_1-C_4-alkoxy.

"C_3-C_{15}-carbocyclic group" as used herein denotes a carbocyclic group having 3 to 15 ring carbon atoms, for example a monocyclic group, either cycloaliphatic, such as a C_3-C_8-cycloalkyl, for example cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl, or aromatic, such as phenyl, which can be substituted by one or more, usually one or two, C_1-C_4-alkyl groups, or a bicyclic group, such as a C_8-bicyclic, C_9-bicyclic or C_{10}-bicyclic group, which could be cycloaliphatic or could be aromatic, such as indanyl, indenyl or naphthyl, again any of which can be substituted by one or more, usually one or two, C_1-C_4-alkyl groups . Preferably the C_3-C_{15}-carbocyclic group is a C_3-C_{10}-carbocyclic group, for example cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, phenyl, indanyl or naphthyl. Phenyl is especially preferred. The C_3-C_{15}-carbocyclic group can be substituted or unsubstituted. Preferred substituents include halo, cyano, hydroxy, amino, nitro, carboxy, C_1-C_8-alkyl, C_1-C_8-haloalkyl, C_1-C_8-alkoxy, C_1-C_8-alkylcarbonyl, C_1-C_8-alkylsulfonyl, $-SO_2NH_2$, a C_3-C_{15}-carbocyclic group and a 5- to 12-membered heterocyclic group having at least one ring heteroatom selected from nitrogen, oxygen and sulphur. "C_3-C_{15}-carbocyclic group" is most especially unsubstituted phenyl.

"C_3-C_8-cycloalkyl" as used herein may be, for example, cyclopropyl, cyclobutyl, cyclopentyl, methylcyclopentyl, cyclohexyl, methylcyclohexyl, dimethylcyclohexyl, cycloheptyl, bicycloheptyl, cyclooctyl and bicyclooctyl. Preferably "C_3-C_8-cycloalkyl" is "C_3-C_6-cycloalkyl".

"C_1-C_8-haloalkyl" as used herein denotes C_1-C_8-alkyl as hereinbefore defined substituted by one or more halogen atoms, preferably one, two or three halogen atoms. Preferably "C_1-C_8-haloalkyl" is "C_1-C_4-haloalkyl".

"C_1-C_8-alkylcarbonyl" as used herein denotes C_1-C_8-alkyl as hereinbefore defined linked to a carbonyl group. Preferably "C_1-C_8-alkylcarbonyl" is "C_1-C_4-alkylcarbonyl".

"C_1-C_8-alkylsulfonyl" as used herein denotes C_1-C_8-alkyl as hereinbefore defined linked to -SO_2-. Preferably "C_1-C_8-alkylsulfonyl" is "C_1-C_4-alkylsulfonyl".

"5- to 12- membered heterocyclic group containing at least one ring heteroatom selected from nitrogen, oxygen and sulphur" as used herein denotes a monoheterocyclic, biheterocyclic or triheterocyclic group, which may be saturated or unsaturated, that has 5 to 12 ring atoms. Monoheterocyclic groups include furyl, pyrrolyl, pyrrolidinyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, thienyl, thiadiazolyl, isothiazolyl, oxadiazolyl, pyridinyl, oxazolyl, isoxazolyl, piperidinyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, piperazinyl, morpholinyl, triazinyl, oxazinyl or thiazolyl. Biheterocyclic groups include benzazolyl, benzimidazolyl, indazolyl and benzothiazolyl. Preferred 5- to 12- membered heterocyclic groups include furyl, pyrrolyl, triazolyl, thienyl, thiadiazolyl, oxazolyl, isoxazolyl, piperidinyl, pyridinyl, pyrazinyl, benzazolyl, benzimidazolyl, indazolyl and benzothiazolyl. The 5- to 12-membered heterocyclic group can be unsubstituted or substituted. Preferred substituents include halo, cyano, oxo, hydroxy, carboxy, nitro, C_1-C_8-alkyl, C_1-C_8-alkylcarbonyl and C_1-C_8-alkoxy optionally substituted by aminocarbonyl.

"Aminocarbonyl" as used herein denotes amino attached through the nitrogen atom to a carbonyl group.

Throughout this specification and in the claims that follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

Preferred compounds include those of formula I in salt or zwitterionic form where
R^1 and R^3 are each independently a C_3-C_{15}-carbocyclic group;
R^2 is hydroxy;
J is a bond;
K is C_1-C_2-alkylene;
L is C_1-C_2-alkylene;
R^4 is C_1-C_4-alkyl;
R^5 is C_1-C_8-alkyl substituted by -OR^6; and
R^6 is a C_3-C_{15}-carbocyclic group.

Especially preferred compounds include those of formula I in salt or zwitterionic form where
R^1 and R^3 are each independently a C_3-C_{10}-carbocyclic group, preferably phenyl;
R^2 is hydroxy;
J is a bond;
K is C_1-C_2-alkylene;
L is C_1-C_2-alkylene;
R^4 is methyl;
R^5 is C_1-C_4-alkyl substituted by -OR^6; and
R^6 is a C_3-C_{10}-carbocyclic group, preferably phenyl.

The compounds of formula I are quaternary ammonium salts. Suitable counter ions are pharmaceutically acceptable counter ions including, for example, fluoride, chloride, bromide, iodide, nitrate, sulfate, phosphate, formate, acetate, trifluoroacetate, propionate, butyrate, lactate, citrate, tartrate, malate, maleate, succinate, benzoate, p-chlorobenzoate, diphenyl-acetate or triphenylacetate, o-hydroxybenzoate, p-hydroxybenzoate, 1-hydroxynaphthalene-2-carboxylate, 3-hydroxynaphthalene-2-carboxylate, methanesulfonate and benzenesulfonate.

Compounds of formula I that contain a basic centre are capable of forming acid addition salts, particularly pharmaceutically acceptable acid addition salts. Pharmaceutically acceptable acid addition salts of the compound of formula I include those of inorganic acids, for example, hydrohalic acids such as hydrofluoric acid, hydrochloric acid, hydrobromic acid or hydroiodic acid, nitric acid, sulfuric acid, phosphoric acid; and organic acids, for example aliphatic monocarboxylic acids such as formic acid, acetic acid, trifluoroacetic acid, propionic acid and butyric acid, aliphatic hydroxy acids such as lactic acid, citric acid, tartaric acid or malic acid, dicarboxylic acids such as maleic acid or succinic acid, aromatic carboxylic acids such as benzoic acid, p-chlorobenzoic acid, diphenylacetic acid or triphenylacetic acid, aromatic hydroxy acids such as o-hydroxybenzoic acid, p-hydroxybenzoic acid, 1-hydroxynaphthalene-2-carboxylic acid or 3-hydroxynaphthalene-2-carboxylic acid, and sulfonic acids such as methanesulfonic acid or benzenesulfonic acid. These salts may be prepared from compounds of formula I by known salt-forming procedures.

Compounds of formula I which contain acidic e.g. carboxyl groups, are also capable of forming salts with bases, in particular pharmaceutically acceptable bases such as those well known in the art; suitable such salts include metal salts, particularly alkali metal or alkaline earth metal salts such as sodium, potassium, magnesium or calcium salts, or salts with ammonia or pharmaceutically acceptable organic amines or heterocyclic bases such as

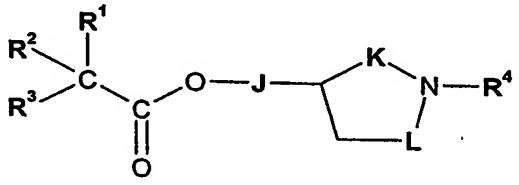
ethanolamines, benzylamines or pyridine. These salts may be prepared from compounds of formula I by known salt-forming procedures.

In those compounds where there is one or more chiral centre the compounds exist in individual optically active isomeric forms or as mixtures thereof, e.g. as racemic or diastereomeric mixtures. The present invention embraces both individual optically active R and S isomers as well as mixtures, e.g. racemic or diastereomeric mixtures, thereof.

Specific especially preferred compounds of the invention are those described hereinafter in the Examples.

The invention also provides a process for the preparation of compounds of formula I which comprises

(i) reacting a compound of formula II



II

or a protected form thereof where R^1, R^2, R^3, R^4, J, K and L are as hereinbefore defined, with a compound of formula III

III

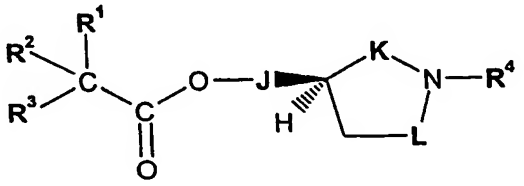
where R^5 is as hereinbefore defined and X is chloro, bromo or iodo; and

(ii) recovering the product in salt or zwitterionic form.

The process may be effected using known procedures for reacting saturated N-heterocyclic esters with halogenides or analogously as hereinafter described in the Examples. The reaction is conveniently carried out in an organic solvent, for example dimethylsulphoxide (DMSO). The reaction is carried out at a temperature between 20° C to 120° C, conveniently between room temperature and 80° C.

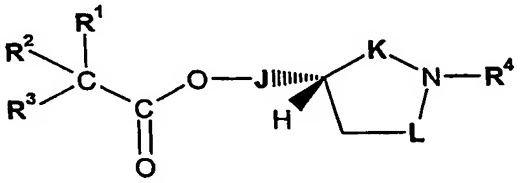
When a compound of formula II is a single enantiomer or is achiral, alkylation of the tertiary amine to give a compound of formula I results in a mixture of two diastereoisomers. These isomers may be separated by conventional techniques, e.g. by fractional crystallization or column chromatography.

Compounds of formula II may exist in individual optically active isomeric forms or as mixtures thereof, e.g. as racemic or diastereomeric mixtures. Preferred compounds of formula II are compounds of formula IIa or IIb



IIa

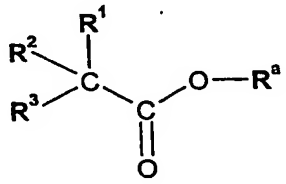
or



IIb

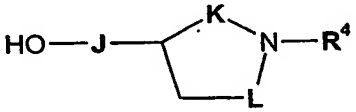
or a protected form thereof where R^1, R^2, R^3, R^4, J, K and L are as hereinbefore defined.

Compounds of formula II are known or may be prepared by reacting a compound of formula IV



IV

or a protected form thereof where R^1, R^2 and R^3 are as hereinbefore defined and R^a is C_1-C_4-alkyl, with a compound of formula V



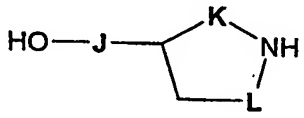
V

where R^4, J, K and L are as hereinbefore defined. This reaction may be effected using known procedures for reacting carboxylic esters with alcohols or analogously as hereinafter described in the Examples.. The reaction is conveniently carried out in an organic solvent, for example cyclohexane, preferably in the presence of sodium and in an inert atmosphere such as argon. The reaction may be carried out at a temperature between 40° C to 120° C, but preferably under reflux conditions.

Compounds of formula III are known or may be prepared by known procedures.

Compounds of formula IV are known or may be prepared by known procedures.

Compounds of formula V are known or may be prepared by alkylating the corresponding secondary amine. For example compounds of formula V where R^4 is methyl may be prepared by reacting a compound of formula VI



VI

where J, K and L are as hereinbefore defined with formaldehyde in the presence of formic acid. The reaction is conveniently carried out in a solvent, for example water, at a temperature from 40° C to 120° C, but preferably about 80° C.

Compounds of formula VI are known or may be prepared by known procedures.

Where reference is made herein to protected functional groups or to protecting groups, the protecting groups may be chosen in accordance with the nature of the functional group, for example as described in Protective Groups in Organic Synthesis, T.W. Greene and P.G.M. Wuts, John Wiley & Sons Inc, Third Edition, 1999, which reference also describes procedures suitable for replacement of the protecting groups by hydrogen.

Compounds of formula I are quaternary ammonium salts and may be converted between different salt forms using ion exchange chromatography. The compounds can be obtained in the form of hydrates or solvates containing a solvent used for crystallization. Compounds of formula I can be recovered from reaction mixtures and purified using known methods. The compounds are initially isolated as diastereomeric mixtures however in most cases they are preferably used in pharmaceutical compositions of the invention as single enantiomers.

Compounds of formula I in pharmaceutically acceptable salt or zwitterionic form, hereinafter referred to alternatively as agents of the invention, are useful as pharmaceuticals. Accordingly the invention also provides a compound of formula I in pharmaceutically acceptable salt or zwitterionic form for use as a pharmaceutical. The agents of the invention act as muscarinic antagonists, particularly muscarinic M3 receptor antagonists thereby inhibiting the infiltration and activation of inflammatory cells, particularly eosinophils, and inhibiting allergic response.

The affinity (Ki) of agents of the invention at the human muscarinic acetylcholine M3 receptor can be determined in a competitive filtration binding assay with the radio-labelled antagonist [^{3}H] n-methyl scopolamine methyl chloride (NMS):

Membranes prepared from CHO cells stably transfected with human M3 receptor at 10 μg protein/ well were incubated with serial dilutions of the agents of the invention, [^{3}H]NMS at Kd concentration (0.25 nM) and assay buffer (20 mM HEPES, 1 mM $MgCl_2$ at pH 7.4) for 17 hours at room temperature. The assay is carried out in a 250 μL final volume, in the presence of a final dimethyl sulfoxide concentration of 1%. Total binding of [^{3}H]NMS is determined in the absence of the agents of the invention with a corresponding substituted volume of assay buffer. Non-specific binding of [^{3}H] NMS was determined in the presence of 300 nM ipratropium bromide. Following the incubation period, the membranes were harvested onto a Unifilter™ GF/B filter plate containing 0.05 % polyethyleneimine, using a Brandel™ filtration harvester 9600. Filter plates are dried for two hours at 35°C before the addition of Microscint™ 'O' cocktail, and are read on a Packard Topcount™ scintillator using a ^{3}H-Scintillation protocol. All IC50s are calculated with the aid of XL-Fit graph package and K_i values are derived using the Cheng-Prusoff correction (Cheng Y., Prusoff W. H. (1973) *Biochem. Pharmacol.* 22 3099-3109).

The compounds of the Examples hereinbelow generally have IC_{50} values below 1 μM in the above assay. For instance, the compounds of Examples 1a, 1b, 1c and 1d have M3 K_i values of 0.36, 0.25, 1.7 and 3.0 nM respectively.

Having regard to their inhibition of binding to M3, agents of the invention are useful in the treatment of conditions mediated by the muscarinic M3 receptor, particularly those associated with increased parasympathetic tone leading to, for example, excessive glandular secretion or smooth muscle contraction. Treatment in accordance with the invention may be symptomatic or prophylactic.

Having regard to their antimuscarinic activity, the agents of the invention are useful in the relaxation of bronchial smooth muscle and the relief of bronchoconstriction. Relief of bronchoconstriction can be measured in models such as the in vivo plethysmography models of Chong et al, *J. Pharmacol. Toxicol. Methods* 1998, 39, 163, Hammelmann et al, *Am. J. Respir. Crit. Care Med.*, 1997, 156, 766 and analogous models. The agents of the invention are therefore useful in the treatment of obstructive or inflammatory airways diseases. In view of their long duration of action, it is possible to administer the agents of the invention once-a-day in the treatment of such diseases. In another aspect, agents of the invention commonly exhibit characteristics indicating a low incidence of side effects commonly encountered with β_2 agonists such as tachycardia, tremor and restlessness, such agents accordingly being suitable for

use in on demand (rescue) treatment as well as prophylactic treatment of obstructive or inflammatory airways diseases.

Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome".)

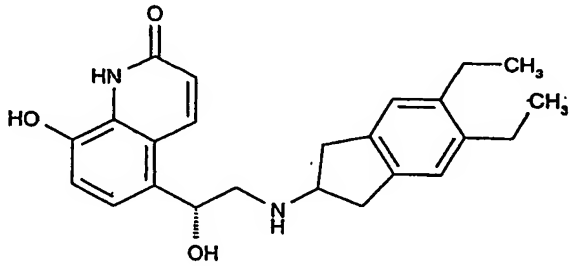
Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e. therapy for or intended to restrict or abort symptomatic attack when it occurs, for example anti-inflammatory (e.g. corticosteroid) or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant from any previously administered symptomatic asthma therapy.

Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary or airways disease (COPD or COAD), including chronic bronchitis, or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, e.g., acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

Having regard to their antimuscarinic activity, the agents of the invention are also useful in the treatment of a condition requiring relaxation of smooth muscle of the uterus or vascular system. They are thus useful for the prevention or alleviation of premature labour pains in pregnancy. They are also useful in the treatment of chronic and acute urticaria, psoriasis, allergic conjunctivitis, actinitis, rhinitis including allergic rhinitis, mastocytosis, urinary disorders such as urinary incontinence, pollakiuria, neurogenic or unstable bladder, cytospasm and chronic cystitis; gastrointestinal disorders such as irritable bowel syndrome, spastic colitis, diverticulitis and peptic ulceration; and cardiovascular disorders such as vagally induced sinus bradycardia.

The agents of the invention are also useful as co-therapeutic agents for use in combination with other drug substances such as anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substances, particularly in the treatment of obstructive or inflammatory airways diseases such as those mentioned hereinbefore, for example as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs. An agent of the invention may be mixed with the other drug substance in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the other drug substance. Accordingly the invention includes a combination of an agent of the invention as hereinbefore described with an anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substance, said agent of the invention and said drug substance being in the same or different pharmaceutical composition. Such anti-inflammatory drugs include steroids, in particular glucocorticosteroids such as budesonide, beclamethasone dipropionate, fluticasone propionate, ciclesonide or mometasone furoate and compounds described in WO 0200679, WO 0288167, WO 0212266 and WO 02100879, LTB4 antagonists such as those described in US 5451700, LTB4 antagonists such as those described in US 5451700, LTD4 antagonists such as montelukast and zafirlukast, PDE4 inhibitors such as Ariflo® (GlaxoSmith Kline), Roflumilast (Byk Gulden),V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), Arofylline (Almirall Prodesfarma), PD189659 (Parke-Davis), AWD-12-281 (Asta Medica), CDC-801 (Celgene) and KW-4490 (Kyowa Hakko Kogyo) and A2a agonists such as those described in EP 1052264, EP 1241176, WO 0023457, WO0077018, WO 0123399, WO 0160835, WO 0194368, WO 0200676, WO 0222630, WO 0296462, WO 0127130, WO 0127131, WO 9602543, WO 9602553, WO 9828319, WO 9924449, WO 9924450, WO 9924451, WO 9938877, WO 9941267, WO 9967263, WO 9967264, WO 9967265, WO 9967266, WO 9417090, EP 409595A2 and WO 0078774 and A2b antagonists such as those described in WO 0242298.

The agents of the invention are also particular useful as co-therapeutic agents for use in combination beta-2 adrenoceptor agonists or corticosteroids. Suitable beta-2 adrenoceptor agonists include salbutamol, terbutaline, salmeterol and, especially, formoterol and pharmaceutically acceptable salts thereof, and compounds (in free or salt or solvate form) of formula I of PCT International patent publication No. WO 0075114, which document is incorporated herein by reference, preferably compounds of the Examples thereof, especially a compound of formula



and pharmaceutically acceptable salts thereof.

Co-therapeutic antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride.

Combinations of agents of the invention and beta-2 adrenoceptor agonists, steroids, PDE4 inhibitors, A2a agonists, A2b antagonists or LTD4 antagonists may be used, for example, in the treatment asthma but particularly COPD.

In accordance with the foregoing, the present invention also provides a method for the treatment of an obstructive or inflammatory airways disease which comprises administering to a subject, particularly a human subject, in need thereof a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore described. In another aspect, the invention provides a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore described for use in the preparation of a medicament for the treatment of an obstructive or inflammatory airways disease.

The agents of the invention may be administered by any appropriate route, e.g. orally, for example in the form of a tablet or capsule; parenterally, for example intravenously; topically to the skin, for example in the treatment of psoriasis; intranasally, for example in the treatment of hay fever; or, preferably, by inhalation, particularly in the treatment of obstructive or

inflammatory airways diseases. In particular, the agents of the invention may be delivered as an inhalable formulation for the treatment of COPD and asthma.

In a further aspect, the invention also provides a pharmaceutical composition comprising a compound of formula I in free form or in the form of a pharmaceutically acceptable salt or solvate thereof, optionally together with a pharmaceutically acceptable diluent or carrier therefor. Such compositions may be prepared using conventional diluents or excipients and techniques known in the galenic art. Thus oral dosage forms may include tablets and capsules. Formulations for topical administration may take the form of creams, ointments, gels or transdermal delivery systems, e.g. patches. Compositions for inhalation may comprise aerosol or other atomizable formulations or dry powder formulations.

When the composition comprises an aerosol formulation, it preferably contains, for example, a hydro-fluoro-alkane (HFA) propellant such as HFA134a or HFA227 or a mixture of these, and may contain one or more co-solvents known in the art such as ethanol (up to 20% by weight), and/or one or more surfactants such as oleic acid or sorbitan trioleate, and/or one or more bulking agents such as lactose. When the composition comprises a dry powder formulation, it preferably contains, for example, the compound of formula I having a particle diameter up to 10 microns, optionally together with a diluent or carrier, such as lactose, of the desired particle size distribution and a compound that helps to protect against product performance deterioration due to moisture. When the composition comprises a nebulised formulation, it preferably contains, for example, the compound of formula I either dissolved, or suspended, in a vehicle containing water, a co-solvent such as ethanol or propylene glycol and a stabiliser, which may be a surfactant.

The invention also includes (A) a compound of formula I as hereinbefore described in free form, or a pharmaceutically acceptable salt or solvate thereof, in inhalable form; (B) an inhalable medicament comprising such a compound in inhalable form together with a pharmaceutically acceptable carrier in inhalable form; (C) a pharmaceutical product comprising such a compound in inhalable form in association with an inhalation device; and (D) an inhalation device containing such a compound in inhalable form.

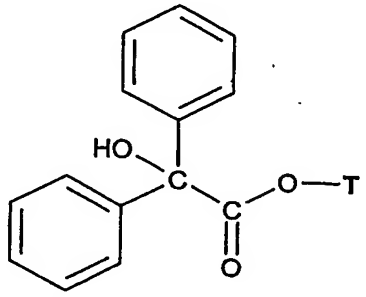
Dosages of agents of the invention employed in practising the present invention will of course vary depending, for example, on the particular condition to be treated, the effect desired and the mode of administration. In general, suitable daily dosages for administration by inhalation

are of the order of 0.0001 to 30 mg/kg, typically 0.01 to 10 mg per patient, while for oral administration suitable daily doses are of the order of 0.01 to 100 mg/kg.

The invention is illustrated by the following Examples.

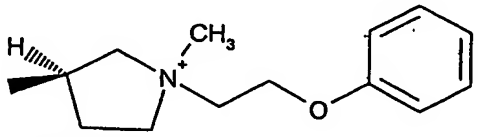
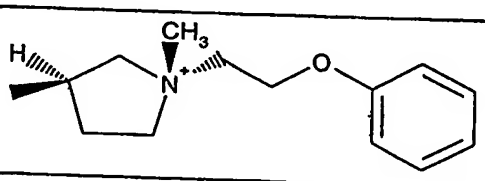
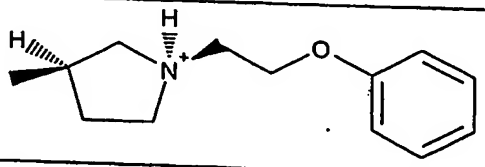
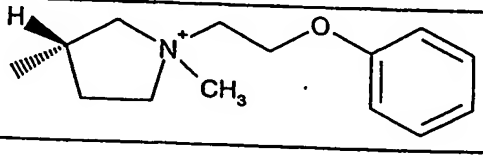
EXAMPLES

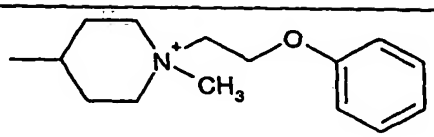
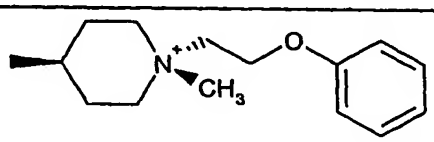
Especially preferred compounds of formula I are also compounds of formula VII



VII

where T is as shown in the Table below, the method of preparation being described hereinafter. All compounds are quaternary ammonium salts. The table also shows mass spectrometry data. In the first column i) describes the stereochemistry of the ring substituent and ii) describes the stereochemistry of the quaternary nitrogen.

Ex.	T	M/s M+
1a		432.29
1b		432.22
1c		432.19
1d		432.20

2a		446.32
2b		446.27

Preparation of Specific Examples

Abbreviations used are as follows: DCM is dichloromethane, DMF is dimethylformamide, and DMSO is dimethylsulphoxide.

Example 1

(1S, 3R)-3-(2-Hydroxy-2, 2-diphenyl-acetoxy)-1-methyl-1-(2-phenoxy-ethyl)-pyrrolidinium bromide (1b) and (1R, 3R)-3-(2-Hydroxy-2, 2-diphenyl-acetoxy)-1-methyl-1-(2-phenoxy-ethyl)-pyrrolidinium bromide (1c)

(R)-1-Methyl-pyrrolidin-3-ol:

To a stirred solution of formaldehyde (75 ml, 1007 mmol, 37% in water) at room temperature is added formic acid (150 ml, 3937 mmol, 99% in water). (R)-Pyrrolidin-3-ol (15 g, 170 mmol) is added dropwise and the reaction mixture is heated to 80°C for 20 hours and then cooled to room temperature. The solvent is removed *in vacuo*. Water (50 ml) is added and washed with DCM (1 x 100 ml). The aqueous solution is basified to pH 14 with sodium hydroxide (solid) and the emulsion extracted with DCM (3 x 100 ml). The combined organic portions are dried over magnesium sulphate and the solvent removed *in vacuo* at 400 mBar. The crude yellow product is distilled under vacuum at 99-101°C, 80-85 mBar to yield the titled compound as a colourless oil.

Hydroxy-diphenyl-acetic acid (R)-1-methyl-pyrrolidin-3-yl ester:

To a stirred solution of (R)-1-Methyl-pyrrolidin-3-ol (8.0 g, 78.4 mmol) and Hydroxy-diphenyl-acetic acid methyl ester (21.0 g, 86.7 mmol) in cyclohexane (200 ml) at 60°C is added sodium (190 mg, 8.3 mmol) under an atmosphere of argon. The reaction mixture is fitted with a Dean-Stark apparatus (to trap the methanol generated) and heated to reflux for 3 hours. The turbid reaction mixture is filtered, washed with cyclohexane (20 ml) and the solvent is removed *in vacuo*. The resulting crude yellow oil is dissolved in ethyl acetate (150 ml) and extracted with 2M HCl (100 ml). The aqueous solution is basified to pH 9 with solid K_2CO_3 and the

resulting emulsion extracted with ethyl acetate (200 ml). The organic portion was dried over $MgSO_4$ and concentrated *in vacuo* to yield the titled compound as a yellow oil.

(1S, 3R)-3-(2-Hydroxy-2, 2-diphenyl-acetoxy)-1-methyl-1-(2-phenoxy-ethyl)-pyrrolidinium bromide and (1R, 3R)-3-(2-Hydroxy-2, 2-diphenyl-acetoxy)-1-methyl-1-(2-phenoxy-ethyl)-pyrrolidinium bromide:

To a stirred solution of Hydroxy-diphenyl-acetic acid (R)-1-methyl-pyrrolidin-3-yl ester (2.17 g, 6.97 mmol) in DMSO (5 ml) is added (2-Bromo-ethoxy)-benzene (2.1 g, 10.45 mmol). The reaction mixture is heated to 50°C for 70 hours. Chloromethyl polystyrene resin (Merrifield Resin, 1 g, 0.84 mmol) and K_2CO_3 (100 mg, 0.7 mmol) is added to scavenge unreacted Hydroxy-diphenyl-acetic acid (R)-1-methyl-pyrrolidin-3-yl ester and the reaction mixture is heated to 40°C for 2 hours. On cooling the reaction mixture is filtered and the solvent is removed *in vacuo*. Purification, using a FlashMaster Personal™ flash chromatography system, on a 70 g Isolute C18™ solid phase extraction cartridge eluting with water:acetonitrile (gradient elution) gives a mixture (1a) of (1S, 3R)-3-(2-Hydroxy-2,2-diphenyl-acetoxy)-1-methyl-1-(2-phenoxy-ethyl)-pyrrolidinium bromide and (1R, 3R)-3-(2-Hydroxy-2,2-diphenyl-acetoxy)-1-methyl-1-(2-phenoxy-ethyl)-pyrrolidinium bromide in approximately equal quantities. Fractional crystallisation from acetonitrile followed by recrystallisation from acetonitrile affords the (1S, 3R)-titled compound (1b). Crystallisation of the concentrated mother liquors from acetone and further recrystallisation also from acetone gives the (1R, 3R)-titled compound (1c).

The compound of Example 1d is prepared using an analogous procedure from the S amino alcohol.

Example 2

Cis and trans-4-(2-Hydroxy-2,2-diphenyl-acetoxy)-1-methyl-1-(2-phenoxy-ethyl)-piperidinium bromide

Hydroxy-diphenyl-acetic-acid 1-methyl-piperidine-4-yl-ester:

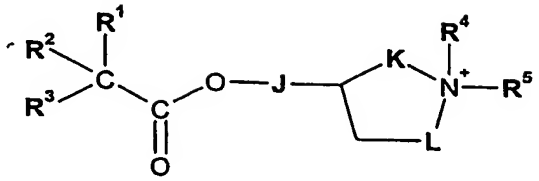
This compound is prepared using the method described in United States patent specification US 3252981.

Cis and trans-4-(2-Hydroxy-2,2-diphenyl-acetoxy)-1-methyl-1-(2-phenoxy-ethyl)-piperidinium bromide:

Hydroxy-diphenyl-acetic-acid 1-methyl-piperidine-4-yl-ester (0.5 g, 1.5 mmol) and (2-Bromo-ethoxy)-benzene (0.37 g, 1.8 mmol) is dissolved in DMF and heated to 40°C for 24 hours. Additional (2-Bromo-ethoxy)-benzene (0.18 g, 0.9 mmol) and 100 mg of potassium carbonate is added and stirring continued at 40°C for another 24 hours. The temperature is raised to 60°C and (2-Bromo-ethoxy)-benzene (0.1 g, 0.5 mmol) is added and stirring continued at this temperature for 24 hours. A further portion of (2-Bromo-ethoxy)-benzene (0.1, 0.5 mmol) is added and stirring continued for 16 hours at 60°C. The reaction mixture is filtered and the solvent evaporated. The resulting oil is taken up in acetonitrile and the product crystallised to give a mixture (2a) of cis and trans isomers. The solid is filtered off and recrystallised twice from acetonitrile to yield the trans diastereoisomer (2b) as a white solid.

CLAIMS

1. A compound of formula I



I

in salt or zwitterionic form wherein

R^1 and R^3 are each independently a C_3-C_{15}-carbocyclic group or a 5- to 12-membered heterocyclic group having at least one ring heteroatom selected from nitrogen, oxygen and sulphur;

R^2 is hydrogen, hydroxy, or C_1-C_4-alkyl optionally substituted by hydroxy;

J and K are both independently C_1-C_2-alkylene,

or one of J and K is a bond and the other is C_1-C_2-alkylene;

L is C_1-C_2-alkylene;

R^4 is C_1-C_4-alkyl;

R^5 is C_1-C_8-alkyl substituted by $-OR^6$, $-O-CO-R^6$ or $-CO-O-R^6$; and

R^6 is C_1-C_8-alkyl, a C_3-C_{15}-carbocyclic group or a 5- to 12-membered heterocyclic group having at least one ring heteroatom selected from nitrogen, oxygen and sulphur.

2. A compound according to claim 1, wherein

R^1 and R^3 are each independently a C_3-C_{15}-carbocyclic group;

R^2 is hydroxy;

J is a bond;

K is C_1-C_2-alkylene;

L is C_1-C_2-alkylene;

R^4 is C_1-C_4-alkyl;

R^5 is C_1-C_8-alkyl substituted by $-OR^6$; and

R^6 is a C_3-C_{15}-carbocyclic group.

3. A compound according to claim 2, wherein

R^1 and R^3 are each independently a C_3-C_{10}-carbocyclic group, preferably phenyl;

R^2 is hydroxy;

J is a bond;

K is C_1-C_2-alkylene;

L is C_1-C_2-alkylene;

R^4 is methyl;
R^5 is C_1-C_4-alkyl substituted by $-OR^6$; and
R^6 is a C_3-C_{10}-carbocyclic group, preferably phenyl.

4. A compound according to claim 1 substantially as described in any one of the Examples.

5. A compound according to any one of the preceding claims in combination with another drug substance which is an anti-inflammatory, a bronchodilator or an antihistamine.

6. A compound according to any one of the preceding claims for use as a pharmaceutical.

7. A pharmaceutical composition comprising as active ingredient a compound according to any one of claims 1 to 5.

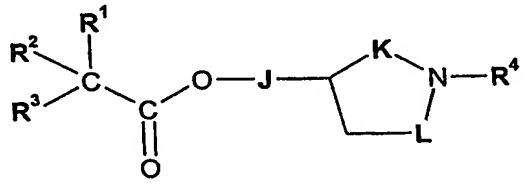
8. The use of a compound according to any one of claims 1 to 5 for the manufacture of a medicament for the treatment of a condition mediated by the muscarinic M3 receptor.

9. Use according to claim 8, in which the condition is an inflammatory or allergic condition, particularly an inflammatory or obstructive airways disease.

10. Use according to claim 8 or 9, in which the compound is a single enantiomer.

11. A process for the preparation of a compound of formula I as claimed in claim 1 which comprises:

(i) reacting a compound of formula II



II

or a protected form thereof where R^1, R^2, R^3, R^4, J, K and L are as defined in claim 1, with a compound of formula III

$$X—R^5 \qquad \text{III}$$

where R^5 is as defined in claim 1 and X is chloro, bromo or iodo; and

(ii) recovering the product in salt or zwitterionic form.